SUBCOMMITTEE ON NATIONAL SECURITY, EMERGING THREATS,
AND INTERNATIONAL RELATIONS
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MEMORANDUM

To: Members of the Subcommittee on National Security, Emerging Threats, and International Relations

From: Christopher Shays
Chairman

Date: May 4, 2006

Subject: Briefing memo for the May 9, 2006 Subcommittee hearing

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Attached find the briefing memo required by Committee rules for the hearing on Tuesday May 9th entitled, *Anthrax Protection: Progress or Problems?* The hearing will convene at 2:00 p.m., room 2154 Rayburn House Office Building.

Congress of the United States

House of Representatives

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MEMORANDUM

To: Members of the Subcommittee on National Security, Emerging Threats, and International Relations

From: Kristine K. Fiorentino

Subject: Briefing Memorandum for the hearing, *Anthrax Protection: Progress or Problems?* scheduled for Tuesday, May 9, 2006, at 2:00 p.m. in room 2154 Rayburn House Office Building.

PURPOSE OF THE HEARING

The purpose of the hearing is to examine what has been done and what is left to do to protect the nation after an anthrax attack. In particular, the hearing will focus on the availability of medical countermeasures, and the government's ability to accurately detect anthrax inside a building.

HEARING ISSUES

1. **How effective is the government's efforts to obtain medical countermeasures?**

2. **What is the status of the government's ability to accurately detect anthrax inside a building?**

BACKGROUND

More than four years ago the nation was attacked with five letters filled with anthrax spores. Since this time, the government has taken steps to protect the nation should another anthrax attack occur. However, concerns remain regarding the availability of medical countermeasures and the ability of the government to accurately detect anthrax inside a building.

In the event people are exposed to aerosolized anthrax spores, the Centers for Disease Control and Prevention (CDC) recommends the administration of 60 days of oral antibiotics in conjunction with a 3-dose regimen (0, 2 weeks, 4 weeks) of anthrax vaccine. The Advisory Committee on Immunization Practices (ACIP) and the John Hopkins Working Group on Civilian Biodefense concluded the best way to prevent inhalation anthrax is by using prolonged antibiotic therapy in conjunction with anthrax vaccine. **(Web Resource 1)**

The Department of Health and Human Services (HHS) purchased 100 million tablets of the antibiotic ciprofloxacin (Cipro) in 2001 for the nation's stockpile. **(Web Resource 2)** On November 4, 2004 HHS announced a contract for $877.5 million to VaxGen, Inc. to manufacture and deliver 75 million doses of a new anthrax vaccine to treat 25 million people after an attack. This vaccine is made by using purified recombinant protective antigen (rPA), "a protein that elicits antibodies that neutralize anthrax toxins, thus providing immunity." **(Web Resource 3)** The vaccine is being evaluated to administer in a three-dose series. As part of the contract, VaxGen must obtain licensure from the Food and Drug Administration (FDA) for using the vaccine in both pre- and post-anthrax exposure. This was the first contract issued under Project BioShield.

HHS had initially funded the development of rPA vaccine in September 2002 through the National Institute of Allergy and Infectious Disease (NIAID) at the National Institutes of Health. NIAID work was based on the Department of Defense research on rPA vaccine over the past 10 years. **(Web Resource 3)**

On May 6, 2005, HHS awarded a $122.7 million contract to BioPort Corporation for the manufacture and delivery of 5 million doses of Anthrax Vaccine Adsorbed (AVA) (also called BIOTHRAX) a licensed anthrax

vaccine to treat 2 million people. **(Web Resource 4)** As of June 2005, over one million doses of this anthrax vaccine were in the national stockpile. **(Web Resource 5)**

DHS also awarded two contracts on September 23, 2005 for the purchase of 10 grams of Anthrax Therapeutics for testing. The awards were given to Human Genome Sciences in the amount of $1,797,372 and the Cangene Corporation in the amount of $422,880. **(Web Resource 6)**

Anthrax Detection

The Subcommittee held a previous hearing on April 5, 2005 entitled, "Assessing Anthrax Detection Methods" to discuss the status of anthrax detection methods. At this hearing, the Government Accountability Office (GAO) provided an update on the status of the government's efforts to implement the recommendations found in their March 2005 report entitled, "Anthrax Detection: Agencies Need to Validate Sampling Activities in Order to Increase Confidence In Negative Results." **(Web Resource 7)**

The science behind anthrax detection results is limited. Detection methods have not been validated and therefore one cannot place too much confidence in the accuracy of the results. It is still unknown if the facilities affected by the 2001 anthrax incidents are completely free of anthrax contamination. However, agencies believe there is little risk now since the samples taken were negative, and no one has presented with symptoms. **(Web Resource 7)**

Validation is especially important since science still does not know what the lethal dose of anthrax for a particular individual is and since anthrax spores are hardy they can last for years to come. **(Web Resource 8)**

"Validation is a formal, empirical process in which an authority determines and certifies the performance characteristics of a given method." **(Web Resource 7)** Anthrax testing done in postal facilities in 2001 was not validated. According to the GAO report, "the lack of validation of agencies' activities, coupled with limitations associated with their targeted sampling strategy, means that negative results may not be reliable." **(Web Resource 7)**

There are several steps involved in the environmental sampling process. They include sampling strategy development, sample collection, sample transportation, sample extraction and sample analysis. These steps have not been validated for anthrax testing. **(Web Resource 7)**

A sampling strategy includes deciding how many samples to collect, where to collect them from and what collection methods to use. The agencies involved in the United States Postal Service (USPS) 2001 anthrax incident chose a targeted strategy. **(Web Resource 7)** Targeted sampling tends to be quicker and inexpensive since it focuses on a particular area instead of ensuring the entire area is tested and there are fewer samples taken. However targeted sampling can be affected by bias and is not a reliable method in deterring the true extent of contamination. **(Web Resource 9)**

The agencies collected samples from specific areas, such as the mail processing area since they were determined to be the most likely places where anthrax would be. However, according to GAO, "Without probability sampling, inferences about a facility's status-that is, whether it was contaminated could not be reliably based on negative results." **(Web Resource 7)**

Probability sampling is based on random selection therefore each item in a population has an equal probability of being chosen. **(Web Resource 9)** When negative results are achieved through probability sampling one can have confidence about the specific level of contaminant in a population. **(Web Resource 7)**

According to the agencies, targeted sampling was used instead of probability sampling because they were limited in the number of samples they could collect since laboratory analytic capacity was limited. **(Web Resource 7)** The agencies and their contractors used different methods to collect samples. USPS used dry swabs to collect samples for the most part, even though these were known to be the lease effective method. CDC and EPA used dry swabs, wet swabs, wet wipes and a high-efficiency particulate air (HEPA) vacuum.

After collecting samples, the agencies had to transport these samples. They followed federal regulations for transporting "infectious substances"

However, these guidelines are meant to prevent an unintentional release of anthrax rather than ensure the samples' biological reliability for testing. It is not known if the anthrax spores were affected by the transportation in terms of their viability (ability to divide and multiply). The effect of temperature and light on spores during transportation has not been studied. Culture analysis is dependent on the spores ability to divide and multiply so tests can determine whether a sample contains anthrax. **(Web Resource 7)**

After transportation, laboratory personnel need to extract the particles from sample material, using extraction fluids and other lab procedures. However, because no sample extraction efficiency data was available, interpreting anthrax analytic results was problematic. **(Web Resource 7)**

After extraction, the material must be analyzed. However, knowledge about the limits of detection for field-based tests was deficient because there were not enough trained personnel to use these methods. **(Web Resource 7)**

GAO Recommendations

The GAO report recommended the Secretary of Homeland Security work with agencies to ensure validation studies of sampling process activities and methods be conducted. Specifically, the GAO recommended the Secretary should:

1. take a lead role in promoting and coordinating the activities of the various agencies that contain the technical expertise related to environmental testing;

2. ensure that a definition of validation is developed and agreed on;

3. guarantee that the overall process of sampling activities, including methods, is validated so that performance characteristics, including limitations, are clearly understood and results can be correctly interpreted;

4. see that appropriate investments are made in empirical studies to develop probability-based sampling strategies that take into account the complexities of indoor environments;

5. ensure that appropriate, prioritized investments are made for all biothreat agents; and make sure that agency policies, procedures and guidelines reflect the results of such efforts. **(Web Resource 7)**

DISCUSSION OF HEARING ISSUES

1. How effective is the government's efforts to obtain medical countermeasures?

While the government has been successful in purchasing antibiotics to treat 40 million people exposed to anthrax spores, the government has faced challenges in obtaining anthrax vaccine. The VaxGen anthrax vaccine was supposed to be in the stockpile by 2007, however VaxGen has admitted delays and will not have the vaccine completed until 2008 or 2009. **(Attachment 1, p. 2)**

Some problems have occurred with the production of the VaxGen vaccine. Tests showed the vaccine was unstable and was losing it's potency within months. HHS requires VaxGen to deliver a product that will be stable enough to sit on a shelf for several years. **(Attachment 1, p. 3)**

VaxGen Inc. also received a warning letter on March 25, 2006 from the Food and Drug Administration stating VaxGen had distributed a document at a promotional booth in connection with the 4th Annual Federal Biodefense Research FY 2006 meeting that contained, "false or misleading statements that represent your product [*Bacillus anthracis* Recombinant Protective Antigen 102 (rPA 102) (anthrax vaccine)] as safe or effective for the purposes for which it is being investigated." **(Attachment 2, p. 1)**

FDA requested that VaxGen, "immediately cease the dissemination of the violative material for your investigational anthrax vaccine" and that VaxGen submit a written response within 10 business days of the letter to explain how they would comply with the request and what steps they would take to, "disseminate truthful, non-misleading, and complete information to the audiences that received the violative material." **(Attachment 2, p. 3)**

Some believe HHS shouldn't have put so much faith in one company to produce the new anthrax vaccine but should have instead allowed for more competition among companies.

The Anthrax Vaccine Adsorbed (AVA) product also remains controversial due to past problems in the manufacturing process such as lot to lot variability, the required six dose regime and servicemembers complaints about side effects and concerns about unknown long term complications from receiving the vaccine. Servicemembers have an option to refuse taking the vaccine and many are doing so. In the past when the anthrax vaccine was mandatory, several servicemembers were court-martialed for refusing to take the anthrax vaccine. When the anthrax vaccine was offered to post office employees after the anthrax attacks in 2001 most decided against taking it and instead chose to take antibiotics. **(Attachment 3, pp. 3-5)**

The controversial history of the anthrax vaccine may make Americans hesitant to take it in the future should an anthrax event occur. Some believe the evidence is not strong enough to show the vaccine will work in cases of inhalation anthrax since most of the research on its effectiveness has been in administering the vaccine prior to anthrax skin exposure (cutaneous anthrax). The one major study of the AVA product showed that is was effective after exposure to inhalation anthrax only if it was used in conjunction with antibiotics. Thus, some believe antibiotics are more effective than anthrax vaccine and present less potential side effects. Animal studies are currently being done to see if the VaxGen vaccine will be effective against inhalation anthrax. **(Attachment 3, pp. 1-2)**

There is also concern the government may be relying too much on anthrax vaccine and too little on ensuring an area is decontaminated. This is noted in Stewart Simonson, Assistant Secretary Office of Public Health Emergency Preparedness, Department of Health and Human Services testimony at a June 14, 2005 Subcommittee hearing, "Anthrax spores are stable in the environment and would have a profound impact if released in an urban population. Therefore, availability of a vaccine may be a critical requirement for repopulation and restoration of the functionality of any exposed area." **(Web Resource 5)**

2. What is the status of the government's ability to accurately detect anthrax inside a building?

The March 2005 GAO report on Anthrax Detection addressed the deficiencies in the government's ability to accurately detect anthrax inside a building. The GAO Report states while DHS and other agencies have applied some lessons learned, conducted conferences, and funded some research, "they do not address the issue of validating all activities related to sampling. Finally the agencies have not made appropriate and prioritized investments to develop and validate all activities related to other biothreat agents." **(Web Resource 7)**

The GAO recommended the Secretary of Homeland Security work with agencies to "ensure that appropriate validation studies of the overall process of sampling activities including the methods, are conducted." **(Web Resource 7)** GAO believes the DHS Secretary needs to take the lead role in ensuring this coordination take place. However, DHS comments to GAO on the report suggest unwillingness on the part of DHS to take the lead in this area. DHS states:

> *"Overall responsibility for coordination has been charged to the Secretary of DHS for future biological attack. However, the lead agencies responsible are outlined in the NPR and HSPD-10. They clearly assign the EPA with the primary responsibility of establishing the strategies, guidelines, and plans for the recovery from a biological attack while HHS has the lead role for any related public health response and guidelines."* **(Web Resource 7)**

DHS explains in the March 2005 GAO report on Anthrax Detection, "Even though DHS is in charge during a biological attack, EPA is primarily responsible for the coordination of the recovery process. So, DHS will coordinate with EPA to ensure appropriate investments are made to explore improved sampling." **(Web Resource 7)** However, it is unclear what steps DHS has taken to improve sampling.

Some believe DHS may be hesitant to validate all the activities related to sampling because of concerns about cost. This is noted in DHS response to the GAO report, "the first steps towards validation must involve defining

the necessary requirements for the sampling process and developing standards from those requirements…the standards development process relies on consensus building, an activity that is often time-consuming and costly." **(Web Resource 7)**

DHS also stated in the GAO report, "The goal is to develop a scientifically defensible sampling strategy and plan prior to a possible biological attack and demonstrate it through planned exercises. So, DHS/S&T [Science and Technology] agrees that a systems approach is needed to fully address the complex problem of a speedier and more cost effective recovery process without significant additional risks to health." Some question how DHS plans to speed up the recovery process and lower costs while at the same time ensure an area will be free of contamination. **(Web Resource 7)**

Should another anthrax incident occur in the future agencies will be faced with the same limitations they were in 2001 in not being able to guarantee an area is free from anthrax contamination since anthrax detection has not been validated. Some believe this is far too great a risk to take since science has not determined the lethal dosage of anthrax.

WITNESS TESTIMONY

Mr. Keith Rhodes, Chief General Accounting Office Technologist, Government Accountability Office, will testify about the government's efforts to implement GAO recommendations regarding anthrax detection and anthrax vaccine production.

Dr. William Winkenwerder, Assistant Secretary of Defense for Health Affairs, Department of Defense will testify about the status of anthrax vaccine and the government's ability to accurately detect anthrax inside a building.

Dr. Gerald Parker, Deputy Assistant Secretary for Public Health Preparedness, Department of Health and Human Services will testify about the status of anthrax medical countermeasures in particular the status of the VaxGen anthrax vaccine.

Dr. Richard Besser, Director of the Office for Terrorism Preparedness and Emergency Response, Centers for Disease Control and Prevention will testify about the government's ability to accurately detect anthrax inside a building.

Dr. Susan Elizabeth George, Deputy Director of Biological Countermeasures Portfolio, Department of Homeland Security (DHS) will testify about the efforts by DHS to implement GAO recommendations regarding anthrax detection.

Ms. Dana Tulis, Deputy Director for the Office of Emergency Management, Environmental Protection Agency will testify about the role EPA plays in anthrax detection.

ATTACHMENTS

1. Justin Gills, "No Hope for Stockpile of New Anthrax Vaccine by November" *The Washington Post,* March 17, 2006.

2. Food and Drug Administration warning letter to VaxGen Inc. (March 24, 2006)

3. Thomas Maier, "Anthrax Vaccine; The Debate" *Newsday,* November 20, 2005.

WEB RESOURCES

1. CDC Website Anthrax Q & A: Preventative Therapy
http://www.bt.cdc.gov/agent/anthrax/faq/preventive.asp

2. HHS Press Release regarding Cipro purchase
http://www.hhs.gov/news/press/2001pres/20011024.html

3. HHS Press Release regarding contract with VaxGen
http://www.hhs.gov/news/press/2004pres/20041104a.html

4. HHS Press Release regarding AVA Anthrax Vaccine purchase
http://www.hhs.gov/news/press/2005pres/20050506.html

5. Testimony from Stewart Simonson, Assistant Secretary, Office of Public Heath Emergency Preparedness, HHS before the Subcommittee on National Security (June 14, 2005).
http://reform.house.gov/UploadedFiles/Simonson%20Testimony.pdf

6. HHS Office of Research and Development Coordination website regarding Project Bioshield Related Procurement Activities.
http://www.hhs.gov/ophep/bioshield/PBPrcrtPrjct.htm

7. GAO Report entitled, "Anthrax Detection: Agencies Need to Validate Sampling Activities in Order to Increase Confidence in Negative Results" (March 2005) GAO-05-251
http://www.gao.gov/

8. Subcommittee hearing transcript for Hearing entitled, *STAMPING OUT ANTHRAX IN USPS FACILITIES: TECHNOLOGIES AND PROTOCOLS FOR BIOAGENT DETECTION"* MAY 19, 2003
http://frwebgate.access.gpo.gov/cgiin/getdoc.cgi?dbname=108_house_hearings&docid=f:89545.wais

9. Non-Probability Sampling website
http://www.statcan.ca/english/edu/power/ch13/non_probability/non_probability.htm

Attachment 1

4 of 190 DOCUMENTS

TechNews

March 17, 2006, Friday

LENGTH: 1549 words

HEADLINE: No Hope for Stockpile of New **Anthrax Vaccine** by November

BYLINE: Justin Gillis; Washington Post Staff Writer

DATELINE: United States

BODY:

The government's $1 billion effort to develop a new **anthrax vaccine** has run into difficulty, with the company in charge of the project reporting failure in a major human test and falling at least a year behind schedule.

Officers at VaxGen Inc. of Brisbane, Calif., said in interviews that they believe they have isolated the problem with their **vaccine** and are well on their way to fixing it. But they acknowledged that they have no hope of meeting a deadline to deliver 25 million doses of the **vaccine** into a national stockpile by November and will default on their contract with the government unless it grants an extension they have requested.

The difficulties appear to confirm predictions on Capitol Hill two years ago that a small company like VaxGen wouldn't be able to meet an aggressive schedule for stockpiling millions of doses of a new **anthrax vaccine.** Until the full stockpile of 75 million doses is ready, the United States would depend on antibiotics to treat a large-scale **anthrax** attack, a strategy that terrorists could overcome by creating antibiotic-resistant **anthrax.**

Administrators at the Health and Human Services Department declined to discuss specifics of the VaxGen contract. But they said that, despite some setbacks, they are building a national defense against anthrax spores, among the most fearsome of bioterror weapons. In particular, they noted, they have already stockpiled enough antibiotics to treat 40 million people after a large-scale attack.

"I think overall we are certainly making progress in our anthrax preparedness program," said Gerald Parker, the chief deputy in an HHS office that manages emergency preparations.

With the VaxGen product delayed, the government recently bought 5 million doses of an older, controversial anthrax vaccine, enough to treat fewer than 2 million people, and hopes to order more when funds are identified.

The anthrax program is emblematic of larger problems in Project BioShield, President Bush's ambitious biowarfare defense program. It's becoming clear that many of the robust national safeguards against biological and radiological terrorism that Bush promised when he got Congress to create BioShield simply won't be ready any time soon. HHS Secretary Michael Leavitt told Congress yesterday that "more can and must be done to aggressively and efficiently implement Project BioShield," and he pledged to reorganize the responsible office.

An injection of federal money into the program, $5.6 billion over a decade plus additional research funds, has piqued the interest of biotechnology companies. But many analysts say the research and development needed to create new products is moving at a glacial pace.

Moreover, most of the nation's biggest drug companies have eschewed the program, seeing little profit but big risk to their reputations if they mess up a high-profile government contract.

The government has thus had to depend on small, financially shaky biotechnology companies. Yet in contrast to the way the Pentagon buys goods, HHS lacks the legal authority to use public funds extensively to shore up companies. It can pay them up to 10 percent of the value of a contract in advance, but that isn't much -- the seemingly mundane tasks of building production lines and perfecting large-scale manufacturing techniques are riddled with pitfalls and can eat up tens or even hundreds of millions in capital.

The companies can get research subsidies early in a project, and they stand to receive hefty government payments at the end, after they deliver a product. But they must finance the expensive middle stages largely on their own. Biotech companies have dubbed that financing gap the "Valley of Death," and it remains to be seen if any of them can get to the other side of it on a major BioShield contract.

Companies have complained bitterly on Capitol Hill that the government has worsened that problem by doing a poor job of laying out its requirements and of issuing contracts expeditiously.

"There should be a sense of expediency and urgency to get these products developed and stockpiled," said Richard B. Hollis, head of Hollis-Eden Pharmaceuticals Inc., a San Diego company that has spent more than $70 million developing a treatment that would be used after a nuclear or radiological explosion. His company has been hammered in the stock market by perceived delays in the government's plans to purchase the drug.

William Hall, an HHS spokesman, said that the government is aware of companies' complaints and is trying to move rapidly but that it also has to take great care in analyzing potential terrorist threats and deciding which treatments and antidotes are worth the taxpayers' money. BioShield's funding "is not a bottomless pit," he said.

Supported by government contracts totaling close to $1 billion, the VaxGen program is a showcase of how BioShield is supposed to work. VaxGen is assigned to produce 75 million doses of vaccine, enough to treat 25 million people after an attack -- roughly equivalent to the entire populations of the Washington and New York metropolitan areas.

That stockpile was originally supposed to be in place by next year. But at the current rate it will be completed no sooner than 2008 or 2009, long after the anthrax attacks of late 2001 prompted the government to promise a better defense.

VaxGen, despite a troubled financial history, has managed to raise $148 million based on its anthrax contracts. It has built a $20 million production facility in South San Francisco, Calif., has hired a staff of 300 and is producing test lots of anthrax vaccine. Money shortages don't appear to have played any role in the recent problems with the vaccine.

But the company's finances are still wobbly, and with at least a year's delay looming before the vaccine is ready, VaxGen's ability to survive long enough to fulfill its contract with the government remains in doubt.

"The so-called Valley of Death is long and hot," said Lance Ignon, VaxGen's vice president for corporate affairs. "How we emerge will be very important -- it will send a strong signal to the rest of the industry."

Efforts are afoot on Capitol Hill to solve the financing problem by creating a biodefense agency with greater contracting powers than HHS. But the proposal has been criticized across the political spectrum because the agency would be exempt from open-government requirements.

VaxGen has been signaling problems in its vaccine program to Wall Street for many months and disclosed in early November that a year's delay was likely,

sending its stock plunging 33 percent. But the scientific details of its problems were unclear before now.

In interviews recently in South San Francisco, VaxGen officers laid out the trouble in detail. They refused to release copies of data from the key human trial that their vaccine flunked, saying the material has not been fully reviewed by the government, but they showed the data to a reporter.

The test, completed last year, revealed an unexpected problem with the strength of the vaccine. Analysis eventually revealed that the vaccine was unstable -- any given batch was losing potency within months. That is a potentially disastrous problem, since the whole point of the vaccine is to sit on a shelf for years, ready for use the moment anthrax is unleashed.

Once they understood it, the VaxGen scientists said, the problem was easy to solve by adding an ingredient. But they can't be certain that fix has worked until they run additional tests, including a human test scheduled to begin later this year. HHS declined to comment on the problem but said VaxGen was required to deliver a product of acceptable stability to the government.

Hall, the HHS spokesman, noted that the government also encountered delays several years ago when it sought to stockpile smallpox vaccine but eventually solved them and acquired enough for every American.

Even when the shelf-life problem is solved, the anthrax vaccine will still be something of an unknown quantity. VaxGen licensed the vaccine from the U.S. Army, which invented it at a laboratory in Frederick, and Army tests show it should work. But naturally occurring anthrax infection is rare, so a new vaccine can't be tested for effectiveness in people. The Food and Drug Administration will have to approve it based on a combination of safety tests in people and effectiveness tests in animals.

With the new vaccine delayed, HHS is stockpiling an older vaccine made by a subsidiary of Emergent Biosolutions Inc., a Gaithersburg company. That vaccine has a checkered history, including lot-to-lot variability and a tendency to cause sore arms and perhaps more serious reactions. Some U.S. soldiers have risked court martial rather than take the vaccine.

If a large anthrax attack happened tomorrow, that vaccine plus antibiotics would be the defenses the government would have to offer people who had been exposed but weren't yet ill. When the same vaccine was offered in 2001 to people potentially exposed to letters containing anthrax spores, many Capitol Hill aides took it, but most postal workers refused, preferring to take their chances using antibiotics alone.

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Attachment 2

Department of Health and Human Services

Public Health Service
Food and Drug Administrati
Center for Biologics Evalua
Research
1401 Rockville Pike
Rockville MD 2O852-1448

March 24, 2006

CBER-06-004

VIA FACSIMIIE AND CERTIFIED MAIIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Ms. Carmen Betancourt
Senior Vice President, Regulatory Affairs
VaxGen Inc.
1000 Marina Boulevard, Suite 200
Brisbane, CA 94005

Re:**[redacted]**
Bacillus anthracis Recombinant Protective Antigen 102 (rPA102) (anthrax vaccine) with Alum

Dear Ms. Betancourt:

The Office of Compliance and Biologics Quality (OCBQ) in the Food and Drug Administration's (FDA's) Center for Biologics Evaluation and Research (CBER) has reviewed a Question and Answer document distributed by your firm's sales representatives at a promotional booth in connection with the 4'h Annual Federal Biodefense Research FY 2006 meeting, October 17-19, 2005, in Washington, DC (copy enclosed) entitled, "Questions and Answers About VaxGen's Anthrax Vaccine Bioshield Contract," for your investigational product Bacillus anthracis Recombinant Protective Antigen 102 (rPA102) (anthrax vaccine) with Alum. The Question and Answer document contains false or misleading statements that represent your product as safe or effective for the purposes for which it is being investigated . As a result, this material misbrands your investigational product under section 502(a) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 352(a), and violates sections 312.6(b) and 312.7 (a) of Title 21 of the Code of Federal Regulations (CFR).

Background

Bacillus anthracis Recombinant Protective Antigen 102 (rPA102) (anthrax vaccine) with Alum is a drug under section 20i(g) of the Act [21 U.S.C.§. 321(g)] and a biologic as defined in section 351(i) of the Public Health Service Act, (PHS Act) [42 U.S.C. § 262].

False or Misleading. Statements

The following statements in your Question and Answer document, which promote the efficacy and safety of your investigational product, are false or misleading:

- "Modem recombinant technology has allowed VaxGen to consistently produce the vaccine at nearly 100 percent purity -- significantly higher than what can be obtained using older technologies such as Bioport's. . . . Bioport's product is less consistent and has greater impurities than VaxGen's rPA102."

  "It is false or misleading for you to make any claims about the consistency. of your vaccine production at this early stage of product development. You have not yet **[redacted]**. Consequently, it is simply premature for you to claim that you can consistently produce this product "at nearly 100% purity."

- "Phase I data from humans indicate that VaxGen's anthrax vaccine induces an - immune response that is comparable to the ones induced by BioPort's vaccine. . . . The immune responses generated by rPAl 02 in humans were comparable to the ones that protected animals from inhalation anthrax."

  This is false or misleading in that during the referenced Phase 1 study **[redacted]** doses of VaxGen's vaccine resulted in immune responses comparable to those elicited by only **[redacted]** doses of Bioport's vaccine. An accurate dose comparison would, at a minimum, be based on testing the same number of doses of each product.

- "VaxGen's vaccine requires significantly fewer doses for protection, and people receiving it will achieve the immune response in a far less time than they would with BioPort's vaccine."

  That statement is false and misleading because it is premature to make any comparative claims about dosages or effectiveness at this early stage in your vaccine's development.

The material mentioned above, generated and disseminated by VaxGen, is labeling for your product. 21 U.S.C. 321(m). Consequently, by bearing false and misleading statements about your investigational product, the material misbrands your investigational product under section 502(a) of the Act and also violates 21 CFR 312.6(b).

In addition, your product is an investigational drug currently under review by the FDA subject to an IND that is in effect. Consequently, the product's labeling "shall not represent that the investigational new drug is safe or effective for the purposes for which it is being investigated." 21 CFR 312 .6(b). Furthermore, you may not promote your investigational product. Specifically, under the investigational new drug regulations, a sponsor or investigator, or any person acting on behalf of a sponsor or investigator, "shall not represent in a promotional context that an investigationa.l new drug is safe or effective for the purposes for which it is under investigation or otherwise promote the drug." 21 CFR 312.7(a). While that provision "is not intended to restrict the full exchange of scientific information concerning the drug," its intent is "to restrict promotional claims of safety or effectiveness of the drug for a use for which it is under investigation . . . ." Id.

Conclusion and Requested Actions

Your material misbrands your investigational anthrax vaccine within the meaning of section 502(a) of the Act and violates 21 CFR 312.6(b) because it is labeling that contains false or misleading statements about the product. The material also violates 21 CFR 312.6(b) because it represents that your product is safe or effective for the purposes for which it is being investigated, and violates 21 CFR 312.7(a) because it promotes your investigational product, and represents in a promotional context that it is safe and effective for the purposes for which it

is under investigation.

OCBQ requests that VaxGen, Inc. immediately cease the dissemination of violative material for your investigational anthrax vaccine such as described above. Please submit a written response within ten (10) business days of the date of this letter, stating whether you intend to comply with this request, listing all violative materials for your investigational anthrax vaccine such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative material. Please direct your response to me at the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and Biologics Quality, HFM- 600, 1401 Rockville Pike, Rockville, Maryland 20852-1448. In all future correspondence regarding this matter, please refer to the IND number and to CBER-06-004. We remind you that only written communications are considered official responses.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your materials for your investigational anthrax vaccine comply with each applicable requirement of the Act and FDA's implementing regulations. Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

/S/

Mary A. Malarkey
Director, Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Attachment 3

Newsday (New York)

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BODY:

America's homeland defense program is spending more than $1 billion on **anthrax vaccines** earmarked for wide civilian use despite uncertainty about their effectiveness and an ongoing debate about potential health problems, Newsday has found.

The **vaccine** stockpiling is a key element of the federal Project BioShield program, which was awarded $5.6 billion in funding in 2004 to develop drugs and **vaccines** to protect Americans against biological and chemical attacks. It constitutes the largest federal effort ever to protect civilians from an **anthrax** attack.

In May, BioPort Corp., the only manufacturer currently licensed in the United States to produce an **anthrax vaccine,** won a $123-million contract to make 5 million new doses for the public. And earlier this month, federal officials doubled their request, saying they wanted to buy another 5 million doses for approximately the same amount.

Last November, another firm, California-based VaxGen, received an $877-million contract, plus up to $69 million in other potential fees, to manufacture 75 million doses of an updated **vaccine.** The product, which still lacks approval by the U.S. Food and Drug Administration, will not be available until 2007, company officials say.

Federal officials say an airborne anthrax attack could kill thousands of people in an urban setting like New York and tout the vaccines as key parts of the civilian defense program.

But while a body of scientific research shows that the current vaccine is effective if administered before skin exposure to anthrax - and the rate of serious side effects is comparable to other common vaccines - several public health experts have raised questions about the vaccine's safety and whether it would work following an airborne attack.

David Ozonoff, a professor at Boston University's School of Public Health, said there was "scant" evidence the vaccine will work to treat people who inhale the airborne spores. He said studies show antibiotics as the most effective treatment, and that the vaccine could cause potentially serious health problems among civilians.

"The number of doses they are amassing is wildly out of proportion to any possible threat from anthrax," Ozonoff said. "What the benefits are is very unclear and there are always [health] risks ... when you vaccinate a whole lot of people."

Hillel W. Cohen, an epidemiologist at the Albert Einstein College of Medicine in the Bronx, agreed.

"The only possible benefit of a vaccine is if there's a danger of exposure and that danger is small because of the technological hurdles of weaponizing anthrax," Cohen said. " ... It's not something you can do in your basement."

If an anthrax attack were to occur today, the nation would rely on stocks of the BioPort vaccine, which, like the VaxGen product, would be provided in combination with antibiotics.

The only major study of the use of the BioPort vaccine following inhalation exposure found it ineffective on laboratory animals unless used in conjunction with antibiotics.

VaxGen also is conducting animal studies of its vaccine, but company officials say they are not yet certain it will work safely and effectively on humans exposed to airborne anthrax attacks.

"We'd hopefully achieve a high level of protection, and the alternative is severe disease," said Harry Keyserling, a pediatrics professor at Emory University School of Medicine in Atlanta and a key researcher in early VaxGen trials.

Still, several prominent members of Congress are skeptical of the amount of federal money going to VaxGen.

"I do question the BioShield acquisition strategy being pursued that bets 800 million dollars on an untested vaccine ... ," said Rep. Christopher Shays (R-Conn.), chairman of the House Subcommittee on National Security, Emerging Threats and International Relations.

"In the event of an attack, we need to know the vaccines and medicines in the national stockpile are the best modern science can produce," Shays said.

The issue of whether the vaccines themselves may cause health problems, and even death, also remains in dispute.

In documents of the FDA, Newsday found reports of more deaths and serious health problems among anthrax vaccine takers than previously reported.

Until late last year, the FDA had listed reports of six deaths and 1,850 "adverse" reactions since 1990, ranging from minor redness at the inoculation site to severe cardiovascular and respiratory system problems, that "possibly" were caused by the BioPort vaccine. The government's monitoring system collects voluntary reports of illness, but does not determine exact causes.

But in a little-noticed report issued in December, the FDA said 16 deaths were possibly linked to the BioPort vaccine. After Newsday asked about other fatalities cited in FDA filings, the agency upped the total number of fatalities possibly linked to the vaccine to 21 - including one the agency said had been "incorrectly coded" in its database.

The same report tallied more than 4,100 illnesses, including 347 it characterized as "serious," as possibly associated with the vaccine.

Government officials say the rate of serious illness associated with anthrax injections is lower than that for other common vaccines such as influenza, smallpox, tetanus, diphtheria and hepatitis.

About 9 percent of all health problems tied to the BioPort vaccine are considered "serious," compared to 14 percent for the other vaccines combined, said the FDA.

"This vaccine is as safe as any," said Kim Brennen Root, a spokeswoman for BioPort, of Lansing, Mich.

Although humans can contract anthrax poisoning through breaks in the skin or the gastrointestinal system, the civilian vaccine program is focused on post-exposure treatment of the deadliest form, inhaled anthrax. Initial symptoms of inhalation anthrax include mild fever and muscle aches, but shock, severe

breathing problems and often meningitis then develop, according to the federal Centers for Disease Control and Prevention.

The BioPort vaccine contains proteins from the anthrax bacteria called "protective antigen," and once in the bloodstream the vaccine makes the body produce antibodies to the antigen, so the bacteria can't produce the anthrax disease. The VaxGen product would work in a similar manner but with technology utilizing new combinations of genetic material.

Under current plans, contaminated civilians, along with others who suspect they were exposed, would be offered a regimen of antibiotics followed by several injections of vaccine.

But while BioPort's FDA license authorizes the vaccine as a preventative against anthrax contracted through skin exposure, federal officials have begun efforts to expand that authorization to cover inhalation anthrax suffered by civilians.

Under the expanded powers in Project BioShield, the BioPort vaccine could be used following an airborne anthrax attack, even without a federal license for that use. The VaxGen product also could be administered to civilians, even if it were still unlicensed.

Federal officials say the catastrophic potential of an anthrax attack would justify any available medical weapon.

"We know that the consequences of such use could be very grave," the Department of Homeland Security said of the possibility of an anthrax attack. But data about whether either of the vaccines would be effective in treating inhalation anthrax victims are scarce.

As the primary evidence that its vaccine would work for post-exposure, BioPort cited a 1993 study in the Journal of Infectious Diseases that was sparked by concerns about anthrax attacks during the Persian Gulf War.

Tested on monkeys

The researchers, led by Arthur Friedlander of the Army Medical Research Institute of Infectious Diseases at Fort Detrick in Frederick, Md., exposed six groups of 10 Rhesus monkeys each to anthrax contained in a spray. Subsequent treatment included the BioPort vaccine by itself, the vaccine in combination with antibiotics or antibiotics alone. Members of a control group received only saline.

The untreated monkeys had a death rate of 90 percent, while 80 percent of the monkeys given only the anthrax vaccine died. The groups treated with the antibiotics Ciprofloxacin or Doxycycline showed death rates of 11 percent and 10 percent, respectively. Another group of animals took a combination of Doxycycline and the vaccine. All survived.

"This suggests that antibiotic treatment, begun early after exposure, prevented the infection from fully developing," the study said, adding that the vaccine "may provide an additional degree of protection against relapse" by killing spores remaining in the body after antibiotic treatment.

"We know that antibiotics treat the symptoms of anthrax, but antibiotics don't kill the spores," said Root, the BioPort spokeswoman.

Beyond that, Friedlander said, the vaccine's effectiveness in treating humans already exposed to anthrax spores remains uncertain.

The vaccine was "not meant to be given after exposure," Friedlander said in an interview. "The vaccine alone doesn't protect and we wouldn't expect it to protect" those contaminated with anthrax.

In touting their vaccine, VaxGen officials also note the limits of antibiotics.

Lance Ignon, VaxGen's vice president of corporate affairs, noted CDC recommendations that anthrax patients take antibiotics for only up to 60 days. He

said patients often don't follow the prescribed schedule, while others develop resistance to antibiotics over time or cannot tolerate them long-term.

Beyond the unanswered questions about efficacy, there is debate about whether the vaccines themselves are dangerous. Some activists and military personnel argue that the government is moving too quickly with plans for a civilian vaccination program, without assurances that the BioPort and VaxGen vaccines won't cause serious health problems.

"There's been a tremendous amount of spin by the government," said Meryl Nass, a physician in Maine and director of the Alliance for Human Research Protection, an advocacy group that has been a long-time critic of the anthrax vaccine program.

Several deaths reported

The BioPort vaccine was first licensed in 1970, primarily for use by agricultural workers in danger of skin exposure to anthrax from animals. The vaccine's health effects have been studied extensively in recent years, beginning with the 1991 Gulf War when thousands of U.S. troops rolled up their sleeves for injections.

Most studies have found low levels of serious illness, although allegations of severe health problems, including several deaths, are detailed in at least one federal report and in several lawsuits.

A 2002 study by the National Academies' Institute of Medicine examined the cases of people who took a total of nearly 2 million doses of the vaccine, primarily in the late 1990s.

Researchers pored over illness reports in examining possible patterns of long-term health problems and gender differences in reactions to the vaccine. They said "limited scientific data" suggested that the vaccine with antibiotics "could provide post-exposure protection" from inhaled anthrax spores. The vaccine, they said, was "sufficiently safe and effective."

In 2003, a study by academics from universities including George Washington in Washington, D.C., and Johns Hopkins in Baltimore reviewed health problems reported by some of the 500,000 military personnel who took the vaccine between 1998 and 2001.

The lead researcher, John Sever of George Washington, said in an interview that the inquiry could find no "unexpectedly high rate" of serious adverse reaction to the vaccine. The study found six known deaths at that time were either "unrelated" to the vaccine or "unclassifiable."

In 2002, however, a U.S. General Accounting Office study of Air National Guard and Air Force Reserve members who took the vaccine revealed that 84 percent reported some adverse reaction - more than double the approximately 30 percent rate reported to the FDA and included in BioPort's packaging at the time. The preponderance were minor, but almost 20 percent were considered serious - chills, fever, nausea and dizziness, with some symptoms lasting more than seven days, the GAO said.

"The implications were that the vaccine was part of the problem of getting sick, and we recommended that they should be following up," said Nancy Kingsbury, who oversaw the GAO study.

The Army rejected the GAO's call for more active surveillance, saying it already kept track of and studied health problems linked to anthrax vaccinations.

Defense Department records show that Army Reservist Spc. Rachel Lacy took vaccinations for anthrax and smallpox at Fort McCoy in Wisconsin, while preparing in March 2003 for overseas deployment. Subsequently, Lacy developed pulmonary and neurological problems that led to inflammation of her lungs. She died the following month.

Lacy's father, Moses, said he believes the combination of vaccinations overwhelmed his daughter. "I do think the anthrax vaccine contributed to my daughter's death," he said.

After reviewing Lacy's case, two federal panels said the evidence "favored a causal relationship" between her death and the vaccines, although they could not establish a conclusive link.

Root, the BioPort spokeswoman, denied any link between Lacy's death and the vaccine.

Other U.S. service members have cited the vaccine's alleged ill effects in lawsuits challenging the military's compulsory use of the BioPort vaccine. Hundreds of troops have refused to undergo the vaccine regimen, and some have faced court-martial.

Three advocacy groups have filed court papers contending that the FDA improperly granted "emergency authorization" for the military to use the vaccine against possible airborne anthrax attacks, and ignored evidence it was unsafe.

Last year, U.S. District Judge Emmet Sullivan, of Washington, D.C., temporarily halted the military program, questioning the FDA's approval of the vaccine for inhalation anthrax cases. Sullivan later allowed the revival of the inoculation program, after the military made it voluntary.

Some health problems, including headaches and fatigue, also have cropped up in early trials of the VaxGen vaccine, company officials said. However, VaxGen chief executive Lance Gordon called the reported health problems "not significant" because of the small initial testing sample.

But BioPort's vice president of medical affairs, Tom Waytes, emphasized VaxGen's early difficulties and said it was time for them "to go back to the drawing board."

Despite the safety debate, BioPort and VaxGen continue to vie for the $5.6 billion in Project BioShield money.

This year, BioPort said it has used Jerome Hauer, former acting assistant secretary of the HHS Office of Public Health and Emergency Preparedness, as a lobbyist in Washington.

Last year, BioPort hired Louis Sullivan, the former HHS secretary under President George H.W. Bush, as a consultant to help land a new federal contract for its anthrax vaccine.

Sullivan said he set up a meeting for the company with government scientists in October 2004. The following month, BioPort announced it would be manufacturing 5 million anthrax vaccine doses for the civilian stockpile.

How the vaccine works: In general, the anthrax vaccine works the same way as tetanus, rabies and other inoculations.

(A) A vaccine is made from an antigen isolated or produced from the disease-causing organism. In the case of anthrax, the existing vaccine is culled from proteins in the bacteria and (B) injected into the bloodstream. (C) Once it recognizes the antigen, T cells in the immune system trigger B cells to neutralize it and another type of T cells to kill it.

The process produces memory cells that remain ready to mount a quick response against subsequent infection from the same agent. That's why, for example, a childhood vaccination generally protects against a disease for a lifetime.

How it's taken

As a preventative, it is taken in six does of 0.5 milliliters each over an 18-month period. For those already exposed, treatment is antibiotics with three doses of vaccine.

Side effects

Mild: Soreness, muscle and joint aches, headaches, chills, fever, fatigue and nausea.

Severe: May range from serious allergic reaction to rarely, death.

Anthrax, in brief

Anthrax spores exist all over the world and become dangerous only when they make contact with human blood, organs and tissues. There are three types of anthrax exposure:

1: CUTANEOUS

· Bacteria enter through a break in the skin.

· Handling contaminated animal products, such as meat, wool or hides.

Death is rare if antibiotic therapy is given.

2: GASTROINTESTINAL

· Eating raw, undercooked, contaminated meat.*

Death in 25% to 60% of cases.

3: INHALATIONAL

· Inhaling at least a deep breath of anthrax spores.

If left untreated, death rate is almost 100%; even when treated, 45% to 80% of patient's die.

1.3 million Number of military personnel who have taken vaccines for anthrax since 1990

5 million+ Number of individual doses supplied since 1990

$123 million Amount BioPort Corp. of Lansing, Mich., is being paid to make 5 million new doses of its vaccine.

$877 million+ Amount VaxGen, Inc., of Brisbane, Calif., is being paid to develop 75 million doses of an updated vaccine.

SOURCES: National Health Museum, Department of Defense, Centers for Disease Control and Prevention, Food and Drug Administration, Anthrax Vaccine Immunization Program

Researched by J. Stephen Smith

GRAPHIC: AP PHOTOS-1) A Coast Guard investigator gets samples in 2001 from a Florida office where anthrax was discovered. 2) Federal officials are moving ahead withproudction of an anthrax vaccine like the sample, above, fro BioPort Corp. 3) AP PHOTO FOR NEWSDAY-Moses Lacy holds aphoto of his daugher Rachel, who died in 2003 after receiving an anthrax and smallpox vaccination while in the Army reserves. 4) AP PHOTO/ANTHRAX VACCINE IMMUNIZATION PROGRAM-A U.S. Defense Department photo shows the deadly bacteria that lead to anthrax. Newdsay illustration by Rod Eyer and chart researched by J. Stephen Smith - How the vaccine works (see end of text)

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